Remarks

Claims 38 through 74 are pending in this application. Claims 1 through 37 were previously cancelled by Preliminary Amendment. In the Applicants' Response to the Restriction Requirement, Group I containing Claims 38 through 46, 49 through 53, and 74 was elected with traverse. For clarity, Applicants note that this election removed Claim 54 from Group I as provided by the Office due to the absence of variable X = S or SO_2. However, the election should not have added Claim 39 to Group I, due to that claim also lacking variable X = S or SO_2. Applicants acknowledge that the Office has rejoined Claims 59 and 64 through 73 upon execution of a search. As such, Claims 38 through 46, 49 through 53, 59, and 64 through 74 are examined in the current Office Action.

The Office indicates that Applicants' assertion regarding the improper refusal to examine that which Applicants regard as their invention unless the subject matter in a claim lacks unity of invention is unpersuasive because the argument applies to US, not PCT, practice. Applicants duly note that the unity of invention requirement exists under PCT, not US, practice (see PCT Rule 13), making their argument on point. The Office also maintains that the claims in the instant case do not have unity of invention and, therefore, the product, process of making, and process of using claims are not examined together. Applicants understand the Office's point to mean that the claims which include all X variables as filed lack unity of invention, since Claims 38 through 46, 49 through 53, 59, and 64 through 74 which cover compounds and compositions, process for preparing compounds and compositions, and method of using compounds of Formula I when X = S or SO_2 are being examined in the current Office Action.

This paper contains amendments under 37 C.F.R. §1.121. All claims limit variable X to S or SO_2 (see, e.g. Claims 38 and 50). Basis for these amendments can be found, at minimum, at page 2, line 10; page 15, line 10; page 114, line 1 through page 127, line 4; and page 155, line 10 through page 158, line 9 in the specification. Variable Q, in independent Claim 38, now lists particular amino acyl groups. Basis for this amendment can be found, at minimum, at page 13, line 24 through page 14, line 27 in the specification. Claims 40 and 41 are cancelled while Claims 38, 42 through 46, and 50 are amended to eliminate variable p – thereby removing the option for more than one amino acyl – and A and/or further limit variables A, R^{10}, and R^{11}. Basis for these amendments can be found, at minimum, at page 15, lines 1 through 8, 15, and 17 in the specification. Claims 64 and 69 are cancelled. Claims 66 and 71 are now independent claims due to the amendments. The amendment to Claim 74 corrects a typographical error. New claim 75

provides a dependent method claim for treating schizophrenia. Basis for this amendment can be found, at minimum, at page 9, line 2 in the specification.

Additionally, the Office notes that Claims 47, 48, 54 through 58, and 60 through 63 are withdrawn from consideration. In order to hasten prosecution of the instant application, Applicants hereby cancel Claims 47, 48, 54 through 58, and 60 through 63. With respect to now cancelled Claims 62 and 63 containing Formula II, Applicants particularly note that they do not acquiesce to the merits of the Office's assertions regarding Massey et al. (US 5,688,826). Additionally, Applicants cancel Claim 39, which as noted *supra* lacks the variable X = S or SO_2, and all claims dependent thereon (Claims 65, 67, 70, and 72). All cancellations made by Applicants are without prejudice. Applicants retain the right to pursue the subject matter of these claims in a subsequent patent application. Furthermore, Claims 68 and 73 are amended to remove dependency upon now cancelled claims.

Information Disclosure Statement

Upon review of the Patent Application Information Retrieval (PAIR) system, Applicants have determined that the US counterpart applications for WO 99/38839, WO 00/12464, and WO 02/00605 were not provided for the Office's review. The EP counterpart application for WO 03/061698 was, however, provided. The Office has only reviewed the abstract for these documents, including WO 03/061698 for which a counterpart was available. Applicants submit that counterpart applications provide sufficient information on the contents of the cited documents and allow the Office to duly consider the noted references. As such, Applicants request that the Office review the counterpart applications for the cited references and remove the limitation from the 1449 that the documents were considered by the abstract only. To that end, concurrent with this response, Applicants will provide electronic copies of the US counterpart applications for WO 99/38839, WO 00/12464, and WO 02/00605 as noted on the 1449 form and respectfully request the Office to consider these documents as well as the previously submitted EP counterpart to WO 03/061698 in their entirety.

Rejection of Claims 38 through 46, 50, and 74 under 35 §U.S.C 102(e)

Claims 38 through 46, 50, and 74 are rejected under 35 U.S.C §102(e) as allegedly being anticipated by Johnson et al. (WO 03/084610). The U.S. priority date for Johnson et al. of April 3, 2002 allows this reference to qualify as prior art under 35 U.S.C. §102(e) for the present application (see MPEP 706.02(f)(1)I.). Under 35 U.S.C. §102(e), the entire disclosure of an

international application publication having an earlier effective U.S. filing date can be relied on to reject the claims (*Sun Studs, Inc. v. ATA Equip. Leasing, Inc.*, 872 F.2d 978, 983, 10 USPQ2d 1338, 1342 (Fed. Cir. 1989). See MPEP § 706.02(a)). Furthermore, when an international application publication is used to reject claims under 35 U.S.C. §102(e), the disclosure relied on in the rejection must be present in the application publication (see MPEP 2136.02 II.). Here, the Office indicates that Johnson et al. teaches compound LY404039, which anticipates [F]ormula I of Claim 38 because variable p equals 1 in the structure and variable Q equals alanyl. While Johnson et al. mentions peptidyl prodrug forms, preferably L-alanyl prodrugs, for mGlu2/3 agonists that are structurally different from those in the instant application, Applicants assert that Johnson et al. is absent information regarding LY404039 in an alanyl – or other – prodrug form. Since Johnson et al. does not contain the alanyl prodrug form of LY404039, Johnson et al. does not anticipate the rejected claims. The Office's rejection under 35 U.S.C. §102(e) is improper. Applicants, therefore, request withdrawal of this rejection.

Rejection of Claims 49 through 51 under 35 U.S.C. §103(a)

Claims 49 through 51 are rejected under 35 U.S.C §103(a) as allegedly being obvious in view of Johnson et al. (WO 03/084610). Enacted on November 29, 1999, the American Inventors Protection Act (AIPA) added subject matter which was prior art under former 35 U.S.C. §103 via 35 U.S.C. §102(e) as disqualified prior art against the claimed invention if that subject matter and the claimed invention "were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person." See MPEP706.02(l)(1)I. As noted *supra*, the Johnson reference qualifies as prior art under 35 U.S.C. §102(e) for the present application. Both Johnson et al. and the present application were, at the time the invention was made, subject to an obligation of assignment to Eli Lilly and Company. Thus, Johnson et al. is disqualified prior art against the claimed invention, making the rejection under 35 U.S.C. §103(a) improper. Applicants request withdrawal of this rejection.

Rejection of Claims 38 through 46 and 64 through 74 under 35 U.S.C. §112, First Paragraph

Claims 38 through 46 and 64 through 74 are rejected under 35 U.S.C. §112, First Paragraph. The Office states that "the specification, while being enabling for examples 1-13 and 41-43, does not reasonably provide enablement for compounds not encompassed by the election of group I and the species." The Office cites *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) and

provides an analysis for two of the *Wands* factors: breadth of the claims and level of predictability in the art. Applicants will address the Office's points below.

Breadth of the Claims

The Office states that "Claims 38 through 46, 59, and 74, as they are currently written, encompass many compounds" and "the scope that is covered by formula I in claim 38 is much too broad for what is encompassed by the elected group." In particular, the Office notes that variable X can be at least 5 groups when taking into consideration variables R^3 and R^4 and that variable A, which is defined as H-(Q)p- where p is an integer from 1 to 10 and Q is an amino acyl, "encompasses the most compounds." Applicants specifically note that variable X has been restricted in this application to S or SO_2, thereby eliminating variables R^3 and R^4. Since the Office has already stated that the specification is enabled for examples 1-13 and 41-43, which have X = S or SO_2, Applicants expect that this aspect of the Office's concern regarding claim breadth has been obviated. Furthermore, while Applicants do not acquiesce to the merits of the Office's assertions regarding variable A, that variable has been amended in the present claim set to involve a particular list of amino acyl groups noted in the application as filed and to permit selection of only one amino acyl group. In view of these points, Applicants submit that the presently filed claims are enabled.

Level of Predictability in the Art

The Office raises an alleged lack of predictability impacting both compound claims (Claims 38-39) and method claims (Claims 64-73). Applicants will address the Office's assertions regarding these claims in turn below.

Claims 38-39

The Office indicates that "[t]here is no predictability for all of the compounds encompassed by formula [I] in claims 38-39" in view of the Office's interpretation of Monn et al. (J. Med. Chem., 2007, 50, 233-240). In particular, the Office has pointed to the "wildly" varying displacement effect for compounds with different atoms at the 2 position in the bicyclohexane or with substitutions on the carbon at the 2 position of the bicyclohexane being indicative of "no predictability" for the claimed compounds as mGlu2[/3] receptor agonists. While Applicants agree that the displacement data provided for the compounds noted by the Office varies, all such data still demonstrate that the compounds tested inhibit specific binding of the mGlu2/3 receptor antagonist used, warranting further functional assessment of the compounds. The functional assay results demonstrate each compound possesses potent agonist activity in both mGlu2- and

mGlu3-expressing cell lines (see Monn et al., p. 234). While the data for the displacement assay varies, the compounds still exhibit sufficient results to demonstrate specific binding. Therefore, the variability that the Office asserts shows these compounds to have "no predictability" for mGlu2[/3] receptor binding is unfounded. Furthermore, the functional assay, not the displacement assay, actually shows that the noted compounds are mGlu2/3 agonists. Applicants respectfully assert that the displacement data variability – as would be expected – in Monn et al. in no way undermines the predictability of the compounds noted by the Office or the claimed compounds as mGlu2/3 agonists.

Additionally, the Office states that the specification describes assays on pages 160 and 161 that *may* be used to evaluate comparative data for the compounds [emphasis on compounds added]. In view of this statement, it appears that the Office has called into question the assays presented and does not appreciate the data provided for the compounds in the application as filed. First, the Gly/Sar assay demonstrates *in vitro* potency for the compounds. Applicants respectfully direct the Office's attention to page 160, lines 30-31 of the application wherein the compounds of the present invention are noted as generally exhibiting EC_{50} values of less than 5 nM. Second, the *in vivo* exposure assay provided on pages 162 through 163 shows the compounds are absorbed into the blood stream and converted to the active moiety (see Tables 1A and 1B on pages 162 and 163). These assays and the data provided demonstrate that the compounds of the present invention – which are prodrugs of mGlu2/3 agonists – are potent, absorbed into the blood stream, and converted to the active moiety. Applicants assert that this information supports the predictability of these characteristics for the claimed compounds.

Claims 64-73

The Office states that "Claims 64-73 cannot be enabled because there is no support in the specification that they may actually have the function that is claimed in these claims. The specification describes assay on page 160 -161 that *may* be used to evaluate comparative data for the compounds" and "none of the compounds are enabled for the methods of use as cited in claims 64-73 due to lack of testing shown." While Applicants in no way acquiesce to the merits of these assertions by the Office, in order to hasten prosecution of the present application, Applicants have cancelled Claims 64 and 69.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make

or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. (See MPEP 2164.03).

For the remaining method claims, which involve specific neurological and psychiatric disorders, Applicants assert that the instant claims are sufficiently enabled. Applicants respectfully direct the Office's attention to Massey et al. (US 5,666,826; the '826 patent), referred to on page 1 of the application as filed, containing active mGluR2[/3] receptor agonists that are parent compounds for some of the prodrugs provided in the present application. The '826 patent contains a claim to a "method of modulating one or more metabotropic glutamate receptor functions in a warm blooded mammal requiring such treatment, which comprises administering an effective amount of a compound as claimed in claim 1" (see Claim 11). This claim shows the mGluR2[/3] receptor agonists claimed are enabled, at minimum, to modulate one or more metabotropic glutamate receptor functions. According to Massey et al., compounds which modulate the function of these receptors, in particular agonists and antagonists of glutamate, are useful for the treatment of acute and chronic neurodegenerative conditions, and as antipsychotic, anticonvulsant, analgesic, anxiolytic, antidepressant, and anti-emetic agents. Also, as noted *supra*, the present application contains assays and data that demonstrate the claimed compounds, which are prodrugs of mGlu2/3 agonists, are potent, absorbed into the blood stream, and converted to the active moiety. As such, the skilled artisan would expect compounds of the present invention to provide – after absorption and conversion – active mGluR2[/3] receptor agonists useful for modulating one or more metabotropic glutamate receptor functions in a warm blooded mammal requiring such treatment and that, therefore, are useful to treat neurodegenerative conditions and as various therapeutic agents. Furthermore, Applicants note that Monn et al. (J. Med. Chem., 2007, 50, 233-240) – a reference noted by the Office in the present Action – points to numerous references pertaining to mGlu2/3 receptors as novel targets for the treatment of anxiety, schizophrenia, convulsive disorders, Parkinson's disease, pain, and neurodegeneration (see page 233, Introduction). As such, the information available to the skilled artisan via, at minimum, Massey et al. – which is noted in the application – and Monn et al. with its references sufficiently enables the invention. The Office's statements regarding the claims not being enabled due to "no support" for the compounds' claimed function and "due to lack of

testing shown" is unfounded, particularly in view of the information available to the skilled artisan for the claimed methods of treatment with prodrugs of mGluR2[/3] receptor agonists.

Applicants respectfully submit that in view of the above-noted points, the rejection under 35 U.S.C. §112, First Paragraph is improper. Therefore, Applicants request withdrawal of this rejection.

Allowable Subject Matter

Claims 52, 53, and 59 depend on presently rejected Claim 38. Applicants assert that the responses and amendments provided for Claim 38 will overcome the Office's rejections for that claim and will, as a result, obviate the objection to Claims 52, 53, and 59.

Applicants acknowledge the Office's assertion that "examples 1-13 and 41-43 are allowable subject matter."

Applicants have amended the claims to contain only elected subject matter.

Conclusion

Applicants assert that the above-stated remarks overcome the Office's rejections for the noted claims under 35 §U.S.C 102(e), 35 U.S.C. §103(a), and 35 U.S.C. §112, First Paragraph. Applicants courteously solicit reconsideration of these rejections and passage of this case to issuance.

Respectfully submitted,

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